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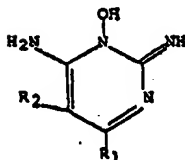
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(54) Composition for inducing and stimulating hair growth, based on pyrimidine derivative

(57) A composition suitable for inducing and stimulating hair growth or for decreasing loss of hair which comprises, in a thickened, essentially aqueous medium, at least one compound of formula (I):



in which:

R₁ denotes a group of formula —N—R_3 in
 —R_4

which R₃ and R₄ are, independently, hydrogen, or an alkyl of 1 to 6 carbon atoms, alkenyl, alkylaryl or cycloalkyl group, or R₃ and R₄, together with the nitrogen atom to which they are attached, form a heterocycle, it being possible for the heterocycle to be substituted, on the carbon atoms, with 1 to 3 alkyl of 1 to 6 carbon atoms, hydroxy or alkoxy groups; and

R₂ denotes hydrogen, or an alkyl of 1 to 6 carbon atoms, alkenyl, alkylalkoxy, cycloalkyl, aryl, alkylaryl, arylalkyl, alkylarylalkyl, alkoxyarylalkyl or haloarylalkyl group,

or a cosmetically or pharmaceutically acceptable acid addition salt thereof, in a concentration at least equal to its solubility limit in the medium.

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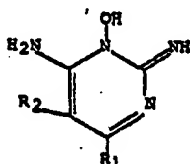
SPECIFICATION

Composition for inducing and stimulating hair growth or for decreasing hair loss, based on pyrimidine derivatives

- 5 The present invention relates to compositions for inducing and stimulating hair growth or for decreasing hair loss, based on pyrimidine derivatives. 5
- Man has about 100,000 to 150,000 hairs and it is normal to lose from 50 to 100 hairs each day. The maintenance of the basic number of hairs results essentially from the fact that the life of a hair is subjected to a cycle, called the pilar cycle, during which the hair is formed, grows and falls before being replaced by a new hair which appears in the same follicle. 10
- In the course of the pilar cycle, three successive phases are observed, the anagen phase, the catagen phase and the telogen phase.
- During the first or anagen phase, the hair passes through an active growth period associated with an intense metabolic activity in the bulb region. 15
- The second or catagen phase is transitory and is marked by a slowing down of mitotic activity. During this phase, the hair undergoes a change, the follicle atrophies and its implantation in the skin appears increasingly shallow.
- The final or telogen phase is a rest period for the follicle and the hair finally falls out, pushed by a newly formed anagen hair. 20
- This constant physical renewal process undergoes a natural change during ageing, the hair becomes finer and the cycles become shorter.
- Alopecia results when this physical renewal process is accelerated or disturbed, i.e. the growth phases become shorter, the passage of hair into the telogen phase is earlier and hairs fall in larger numbers. Successive growth cycles result in increasingly fine and short hair, which is slowly converted into fluff. This phenomenon may lead to baldness. 25
- The pilar cycle depends on many factors which may lead to alopecia. Among these factors are nutritional factors, endocrinal factors and nervous factors. The changes in the different categories of hair may be determined with a trichogram.
- 30 Composition which eliminate or reduce alopecia, especially which induce or stimulate hair growth, have been sought in the cosmetic or pharmaceutical industry for many years.
- To this end, compounds such as 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine and derivatives thereof have already been proposed. Such compounds are described especially in US-A-4,139,619.
- 35 A combination of retinoids with the abovementioned compounds is proposed in WO-A-83/02,558. 35
- Preparations based on 6-amino-1,2-dihydro-1-dihydroxy-2-imino-4-piperidinopyrimidine generally contain water, ethyl alcohol and propylene glycol or mixtures of two of these compounds. However, such compositions have the disadvantage of waxing the hair, increasing its weight and making it oily and sticky. This disadvantage is further enhanced after repeated local applications. 40
- Although such compositions have an efficacy with regard to hair growth, they do not, however, prove to be totally satisfactory from a cosmetic point of view.
- Moreover, the solvent employed to present the active substance in the dissolved form is present in a high proportion and may cause irritation.
- 45 We have discovered that it is possible to increase the efficacy of pyrimidines, having an effect on hair growth, by using these compounds in a concentration at least equal to their solubility limit in thickened aqueous media. 45
- We have observed that such compositions have an activity with regard to inducing and stimulating hair growth and decreasing hair loss. It has noted, in particular, that the efficacy is greater or at least equal to that of previous compositions, at lower doses of active substance and at lower frequencies of application. 50
- The composition of the present invention leads to better bioavailability of the active substance through the skin.
- Moreover, these compositions are particularly stable during storage. Use in the thickened form also permits a good storage as far as the corneous layer is concerned. 55
- Moreover, in comparison with the composition of the prior art, the compositions, which are essentially aqueous, have the advantage of not being irritating and greasy and of not waxing the hair.
- The present invention provides a composition suitable for inducing and stimulating hair growth or for decreasing loss of hair which comprises, in a thickened, essentially aqueous medium, at least one compound of formula (I): 60

(I):

5



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in which:

10

R_1 denotes a group of formula $-N-\begin{matrix} R_3 \\ R_4 \end{matrix}$ in

10

15 which R_3 and R_4 are, independently, hydrogen, or an alkyl of 1 to 6 carbon atoms, alkenyl, alkylaryl or cycloalkyl group, or R_3 and R_4 , together with the nitrogen atom to which they are attached, form a heterocycle, it being possible for the heterocycle to be substituted, on the carbon atoms, with 1 to 3 alkyl of 1 to 6 carbon atoms, hydroxy or alkoxy groups;

15

and R_2 denotes hydrogen or an alkyl of 1 to 6 carbon atoms, alkenyl, alkylalkoxy, cycloalkyl, 20 aryl, alkylaryl, arylalkyl, alkylarylalkyl, alkoxyarylalkyl or haloarylalkyl group, or a cosmetically or pharmaceutically acceptable acid addition salt thereof, in a concentration at least equal to its solubility limit in the medium.

20

In formula (I) the alkyl or alkoxy groups preferably have from 1 to 4 carbon atoms, the alkylene groups preferably have from 2 to 5 carbon atoms and the aryl groups preferably are phenyl. In a preferred embodiment, the concentration of the compound of formula (I) is higher 25 than its solubility limit such that the thickened aqueous medium comprises at least some of the compound of formula (I) in suspension in the form of particles.

25

The compound of formula (I) is preferably in suspension in the form of particles with a size less than $80\text{ }\mu\text{m}$, preferably less than $20\text{ }\mu\text{m}$ and more particularly less than $5\text{ }\mu\text{m}$.

30 In a preferred embodiment the compound of formula (I) is in the micronized form.

30

The compound of formula (I) is advantageously in the form of a crystalline powder obtained, in particular, by grinding it in the dry state in a mechanical mortar until particles, preferably with a mean diameter less than $20\text{ }\mu\text{m}$ and more preferably less than $5\text{ }\mu\text{m}$, are obtained, or by airflow micronization.

35 The essentially aqueous medium advantageously comprises less than 20% of solvent, and preferably from 1 and 10% of solvent.

35

The solvent is preferably a C_1-C_4 alcohol, alkylene glycol, alkylene glycol alkyl ether or dialkylene glycol alkyl ether.

In the compound of formula (I), the heterocycle is advantageously an aziridinyl, azetidiny, 40 pyrrolidinyl, piperidyl, hexahydroazepinyl, heptamethyleneimine, octamethyleneimine, morpholine or 4-(C_1-C_4 alkyl)-piperazinyl group.

40

In particularly preferred compounds of formula (I) R_2 denotes hydrogen and R_1 represents a group of formula

45 R_1 denotes a group of formula $-N-\begin{matrix} R_3 \\ R_4 \end{matrix}$ in

45

in which R_3 and R_4 form a piperidyl ring, and the salts thereof, such as, for example, the sulphate. If R_3 or R_4 is an alkyl group, it advantageously has from 1 to 4 carbon atoms.

50 The particularly preferred compound is 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine, which is also called "Minoxidil" (Trade Mark).

50

A medium with a viscosity greater than 0.4 Pa.s, preferably from 1.5 Pa.s to 10 Pa.s, is a preferred thickened medium.

55 The aqueous suspension medium generally contains thickeners which do not cause agglomeration of the particles of the compound of formula (I). The thickeners are preferably polyacrylic acids crosslinked with a polyfunctional agent such as, more particularly, the products sold under the name "CARBOPOL" (Trade Mark) by GOODRICH, such as Carbop 1 910, 934, 934 P, 940, 941 and 1342, or thickeners resulting from the ionic interaction of a cationic polymer consisting of a copolymer of cellulose or a cellulose derivative grafted with the quaternary ammonium salt 60 of a water-soluble monomer and a carboxylic anionic polymer with an absolute capillary viscosity in dimethylformamide or more than 1, at a concentration of 5% and at 30°C , of less than or equal to 30×10^{-3} Pa.s, the thickener itself having a viscosity greater than or equal to 0.50 Pa.s as determined with an Epprecht-Drage viscometer, module 3, in 1% solution in water at 25°C .

60

65 The cationic polymer which reacts with the anionic polymer is preferably a cationic polymer of

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hydroxyalkyl cellulose grafted, by the radical group, with the quaternary ammonium salt of a water-soluble monomer which is a methacryloylethyltrimethylammonium, methacrylamidopropyltrimethylammonium or dimethyldiallylammonium salt. The carboxylic anionic polymer is preferably a methacrylic acid homopolymer with a molecular weight greater than 20,000, as determined by light scattering, a copolymer of methacrylic acid with a monomer which is a C₁-C₄ alkyl acrylate or methacrylate, acrylamide derivative, maleic acid or C₁-C₄ alkyl monomaleate, N-vinylpyrrolidone or a copolymer of ethylene and maleic anhydride. The weight ratio between the cationic polymer and the carboxylic anionic polymer is generally from 1:5 to 5:1.

The preferred thickeners are products resulting from an ionic interaction of a hydroxyethylcellulose copolymer grafted, by the radical route, with diallyldimethylammonium chloride, such as the products sold under the name "CELQUAT L 200" (Trade Mark) or "H 100" by NATIONAL STARCH, with:

- a copolymer of methacrylic acid and methyl methacrylate, with a capillary viscosity of the order of 15×10^{-3} Pa.s, as determined in a 5% solution in dimethylformamide at 30°C;
- a copolymer of methacrylic acid with ethyl monomaleate, with an absolute capillary viscosity of the order of 13×10^{-3} Pa.s, as determined in a 5% solution in dimethylformamide at 30°C;
- a copolymer of methacrylic acid with butyl methacrylate, the absolute capillary viscosity of which is of the order of 10×10^{-3} Pa.s, as determined in a 5% solution in methanol; or
- a copolymer of methacrylic acid with maleic acid, the absolute capillary viscosity of which is of the order of 16×10^{-3} Pa.s, as determined in a 5% solution in dimethylformamide.

The compound of formula (I) is preferably present in the composition in a proportion of from 0.2 to 5% by weight, preferably from 0.3 to 3% by weight, relative to the total weight of the composition.

The thickening agent is preferably present in the composition in a proportion of from 0.4 to 2%, more preferably from 0.4 to 1.5%, by weight relative to the total weight of the composition.

In addition to the solvent, the composition may optionally contain preservatives, complexing agents, colouring agents, alkalizing or acidifying agents or perfumes.

The pH of the compositions is generally from 4 to 9, and is preferably from 7 to 8.5.

A particularly preferred composition comprises from 0.3 to 3% of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine in water containing from 0.4 to 1.5% of crosslinked polyacrylic acid with a molecular weight of 3,000,000 or alternatively, a thickening agent consisting of hydroxyethylcellulose copolymer grafted by the radical route, with diallyldimethylammonium chloride and methacrylic acid/methyl methacrylate copolymer, and not more than 10% by volume of ethyl alcohol.

The composition may, for example, be prepared by introducing into the thickened medium, the compound of formula (I) in the form of a powder, the particles of which are as defined above, in a proportion sufficient for all or part of the compound of the formula (I) to dissolve in the medium, in a concentration of at least equal to the solubility limit, the undissolved particles remaining in suspension in the medium.

Another possibility comprises preparing a saturated solution of the compound of formula (I) and introducing more compound of formula (I) in the form of particles as defined above, in order to form a suspension.

The proportions indicated are the proportions of the compound of formula (I) present in the total composition either in the dissolved form or suspended in the thickened aqueous medium.

The present invention also provides a cosmetic treatment of the scalp and hair wherein at least one composition as defined above is applied to the scalp or the hair. The treatment method, for example, mainly consists in applying to the alopecic regions of the scalp and hair of an individual, a composition as defined above, for example after washing the scalp and the hair with a shampoo or shortly after shampooing.

The treatment has, in particular, the features of a cosmetic method insofar as it enables the hair or the scalp to be treated in the cosmetic sense of the term, i.e. applying thereto substances which they lack and beautifying them.

Moreover, it may have the features of a therapeutic treatment insofar as it has an effect on biological functions and mechanisms.

The following Examples further illustrate the present invention.

EXAMPLE 1

A suspension medium with the following composition is prepared:

5	Crosslinked polyacrylic acid, M.W.=3 million, sold under the name "CARBOPOL 934" by GOODRICH	1.0 g	5
	2-butoxyethanol	4.5 g	
	2-amino-2-methyl-1-propanol	qs pH	8.5
	Preservative	qs	
10	Water	qs	100.0 g

3 g of micronized 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine, with a mean particle diameter of 4 μ m is then added to the suspension medium and the suspension is then homogenized with a three-roll mill.

The Epprecht-Drage viscosity, module 4, of the composition at 25°C is 7.2 Pa.s.

EXAMPLE 2

A suspension medium with the following composition is prepared:

	Celquat L 200	0.7 g AS	
20	50:50 methacrylic acid: methyl methacrylate copolymer	0.7 g AS	20
	Ethyl alcohol	10% by vol.	
	Ethylene diaminetetraacetic acid	0.02g	
	2-amino-2-methyl-1-propanol	qs pH	7.5
25	Water	qs	100.0 g

3 g of micronized 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine with a mean particle diameter of 4 μ m is then added to this suspension medium and the suspension is homogenized with a three-roll mill.

The Epprecht-Drage viscosity, module 3, of the composition at 25°C is 2.15 Pa.s

EXAMPLE 3

The following composition is prepared:

	Crosslinked polyacrylic acid, MW=3 millions, sold under the name "CARBOPOL 934" by GOODRICH	1 g	
35	Propylene glycol	4.5 g	35
	2-amino-2-methyl-1-propanol	qs pH 7	
	Preservative	qs	
	Water	qs	100 g

1 g of micronized 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine with a mean particle diameter less than 2 microns is then added to this medium and the suspension is then homogenized with a three-roll mill.

It is observed that a part of the particles are dissolved in this medium (approximately 0.25 g), the remaining part staying in suspension.

When this composition is applied to the scalp for a period of three months at a rate of one treatment per day, a significant increase, of the order of 28%, is observed in the number and the density of hairs in the anagen phase.

The Epprecht-Drage viscosity, module 4, of the composition at 25°C is 7.8 Pa.s.

EXAMPLE 4

2 g of micronized 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine with a particle diameter less than 2 μ m is added to the medium in Example 3 and the suspension is homogenized with a three-roll mill.

A significant increase (of the order of 30%) is observed in the number of hairs in the anagen phase, after a 3-month treatment.

The Epprecht-Drage viscosity, module 4, of the composition at 25°C is 7.5 Pa.s.

EXAMPLE 5

0.5 g of micronized 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidin pyrimidine with a particle diameter less than 2 μ m is added to the medium in Example 4 and the suspension is homogenized with a three-roll mill.

As previously, an increase in anagen phase hair is observed.

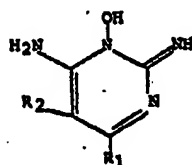
The Epprecht-Drage viscosity, module 4, of the composition at 25°C is 7.5 Pa.s.

EXAMPLES OF FORMULATION NOS. 6 to 15

EXAMPLE No.	6	7	8	9	10	11	12	13	14	15
6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine g	0.5	2	2	1	1.5	3	1	1.5	0.5	0.3
Crosslinked polyacrylic acid g MW = 3,000,000 "Carbopol 934"* MW = 4,000,000 "Carbopol 940"* MW = 1,250,000 "Carbopol 941"* * sold by GOODRICH	0.5	1	1	1	1	1	1	1	1	1
Ethanol g Propylene glycol g Dipropyleneglycol methyl ether g	4.5	4.5	4.5	8	15	18				4.5
Tampon qs pH	7	8.5	8.5	7	7	7	7	7	7	7
Preservative	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Water qs	100	100	100	100	100	100	100	100	100	100
Eppecht-Drage viscosity at 25°C in Pa.s.					10.2					
module 2										
module 3									1.6	
module 4	4.4	8.0	8.0	3.4		4.7	2.5	2.0		7.5
Particle size of the active principle in µm	<2	<20	<2	25-60	60-80	25-60	<2	25-60	60-80	<2

CLAIMS

1. A composition suitable for inducing and stimulating hair growth or for decreasing loss of hair which comprises, in a thickened, essentially aqueous medium, at least one compound of formula (I):



in which:

R_1 denotes a group of formula $-N-R_3$ in

- which R_3 and R_4 are, independently, hydrogen, or an alkyl of 1 to 6 carbon atoms, alkenyl, alkylaryl or cycloalkyl group, or R_3 and R_4 , together with the nitrogen atom to which they are attached, form a heterocycle, it being possible for the heterocycle to be substituted, on the carbon atoms, with 1 to 3 alkyl of 1 to 6 carbon atoms, hydroxy or alkoxy groups; and R_2 denotes hydrogen, or an alkyl of 1 to 6 carbon atoms, alkenyl, alkylalkoxy, cycloalkyl, aryl, alkylaryl, arylalkyl, alkylarylalkyl, alkoxyarylalkyl or haloarylalkyl group, or a cosmetically or pharmaceutically acceptable acid addition salt thereof, in a concentration at least equal to its solubility limit in the medium.
2. A composition according to claim 1 wherein the concentration of the compound of the formula (I) is higher than its solubility limit such that thickened aqueous medium comprises at least some compounds of formula (I) in suspension in the form of particles.
3. A composition according to claim 2 wherein the undissolved compound of formula (I) is present in the form of particles with a mean particle size of less than $80 \mu m$.
4. A composition according to claim 3 wherein the mean particle size is less than $20 \mu m$.
5. A composition according to any one of claims 1 to 4 wherein the compound of formula (I) is present in micronized form.
6. A composition according to any one of claims 1 to 5 wherein the heterocycle is an aziridinyl, azetidiny, pyrrolidinyl, piperidyl, hexahydroazepinyl, heptamethylenimine, octamethylenimine, morpholine or 4-(C_1 - C_6 alkyl)-piperazinyl group.
7. A composition according to claim 6 wherein the compound of formula (I) is 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidino-pyrimidine or a cosmetically or pharmaceutically acid addition salt thereof.
8. A composition according to any one of claims 1 to 7 wherein the compound of formula (I) is present in the composition in the form of particles with a mean particle size of less than $5 \mu m$.
9. A composition according to any one of claims 1 to 8 wherein the thickening agent is polyacrylic acid crosslinked with a polyfunctional agent.
10. A composition according to any one of claims 1 to 8 wherein the thickening agent consists of a product resulting from the ionic interaction of a cationic polymer consisting of a copolymer of cellulose or a cellulose derivative, grafted, with the quaternary ammonium salt of a water-soluble monomer and a carboxylic anionic polymer with an absolute capillary viscosity, in dimethylformamide or methanol, at a concentration of 5% and at $30^\circ C$, of less than or equal to 30×10^{-3} Pa.s, the thickener having an Epprecht-Drage viscosity, module 3, in a 1% solution in water at $25^\circ C$, of greater than or equal to 0.5 Pa.s.
11. A composition according to claim 10 wherein the thickening agent is a product resulting from the ionic interaction of hydroxyalkylcellulose copolymers grafted, by the radical route, with the quaternary ammonium salt of a water-soluble monomer which is a methacryloylethyltrimethylammonium, methacrylamid propyltrimethylammonium, or dimethyldiallylammonium salt and a carboxylic anionic polymer which is a methacrylic acid homopolymer with a molecular weight greater than 20,000, as determined by light scattering, copolymer of methacrylic acid with a monomer which is a C_1 - C_4 alkyl acrylate or methacrylate, acrylamide derivative, maleic acid, C_1 - C_4 alkyl mon maleate, N-vinylpyrrolidone or copolymer of ethylene and maleic anhydride.
12. A composition according to any one of claims 1 to 11 which comprises less than 20% by weight of a solvent which is a C_1 - C_4 alcohol, alkylene glycol, alkylene glycol alkyl ether or dialkylene glycol alkyl ether.
13. A composition according to claim 12 wherein the solvent is present in a proportion of

less than 10% by weight relative to the total weight of the composition.

14. A composition according to any one of claims 1 to 13 wherein the compound of formula (I) is present in a proportion of from 0.2 to 5% by weight relative to the total weight of the composition.

5 15. A composition according to claim 14 wherein the compound of formula (I) is present in a proportion of from 0.3 to 3% by weight. 5

16. A composition according to any one of claims 1 to 15 wherein the thickening agent is present in a proportion of from 0.4 to 2% by weight relative to the total weight of the composition.

10 17. A composition according to claim 16 wherein the thickening agent is present in a proportion of from 0.4 to 1.5% by weight. 10

18. A composition substantially as hereinbefore described in any one of the Examples.

19. A composition according to any one of claims 1 to 18 for use in a medicinal treatment of the control of hair loss, or for inducing and stimulating hair growth.

15 20. A cosmetic treatment of the scalp and hair wherein at least one composition as defined in any one of claims 1 to 18 is applied to the scalp or the hair. 15

21. Use of a compound of formula (I) as defined in claim 1 in the preparation of a composition as defined in any one of claims 1 to 18 for the control of hair loss or for inducing or stimulating hair growth.